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(54) Title: USE OF COPOLYMER-1 FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF OPTIC NEURITIS

(57) Abstract

Use of copolymer-1 to treat visual impairments associated with multiple sclerosis.

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USE OF COPOLYMER-1 FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF OPTIC NEURITIS

FIELD OF INVENTION

The present invention relates to the use of copolymer-1 in treating visual impairments associated with multiple sclerosis.

PRIOR ART

Throughout this application, various references are referred to. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

Multiple sclerosis (MS) is a slow progressive CNS disease characterized by disseminated patches of demyelination in the brain and spinal cord, resulting in multiple and varied neurological symptoms and signs, usually with remissions and exacerbations (relapses). A common symptom prior to diagnosis of MS is some degree of visual impairment, frequently optic neuritis or retrobulbar optic neuritis. Alternatively, these and other visual impairments may only develop after a diagnosis of MS has been confirmed. These symptoms may also develop during the progression of the disease alongside other associated visual problems.

Several studies have concentrated on assessing whether optic neuritis is a reliable predictor of multiple sclerosis (Cohen MM et al., Neurology (1979) 29 208-213, Rizzo JF et al., Neurology (1988) 38 185-199, Beck RW et al., Neurology (1992) 42 1133-1135 and New Eng J Med (1993) 326 581-588).

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433).

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It has been shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317: 408).

SUMMARY OF THE INVENTION

It has recently been observed that patients when treated with copolymer-1 have a lower than expected chance of suffering from visual impairments. This is believed to be of considerable advantage to the general well-being of such patients.

Thus, the present invention relates to the use of copolymer-1 in the manufacture of a medicament for the treatment of visual impairment associated with multiple sclerosis.

In an alternative embodiment the invention relates to the use of copolymer-1 in the manufacture of a medicament for the treatment of optic neuritis.

The present invention includes a method of treating a patient suffering from visual impairment related to multiple sclerosis, comprising administering to said patient a therapeutically effective amount of copolymer-1.

The present invention further includes a method of treating a patient suffering from optic neuritis, comprising administering to said patient a therapeutically effective amount of copolymer-1.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

According to the present invention treatment with copolymer-1 may result in a prevention of any deterioration in visual impairment associated with MS, or in a reduction in the rate of such deterioration. Said treatment may also result in an improvement in vision.

Examples of the types of visual impairment associated with MS include deteriorations in visual acuity, state of the optic disc, pupil reaction, visual field and ocular motility. Particular conditions that are associated with visual impairment in MS include optic neuritis, retrobulbar optic neuritis, diplopia, dimness of vision and scotomas.

Similarly in the treatment of optic neuritis, treatment with copolymer-1 may result in prevention of further episodes of optic neuritis, delaying of further episodes or return vision to an unimpaired state.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in US Patent 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and E-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. As used herein the terms "ambient temperature" and "room temperature" are used to indicate temperatures from about 20°C to about 26°C.

Compositions of use in the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection, preferably copolymer-1 is formulated with mannitol. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients at a dosage of 20mg.

The invention will be exemplified but not necessarily limited to the following Examples.

EXAMPLE 1

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18g), alanine (50g), γ-benzyl glutamate (35g) and trifluoroacetyllysine (83g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01 - 0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried-out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Deprotection of copolymer-1

20g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°-20°C against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5-6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

EXAMPLE 2

Assessment of visual impairment in patients suffering from multiple sclerosis

Patients were recruited into the study having fulfilled the following criteria;
- be 18 to 50 years of age,
- have definite MS as defined by Poser et al. (Ann. Neurol. (1983) 13 227-231),
- be of the relapsing-remitting or relapsing-progressive type when admitted to the trial,
- have objective evidence of neurological disease that reflects predominantly white matter damage, and
- have had at least two well documented attacks in the two-year period leading up to study entry.

Copolymer-1 was administered sub-cutaneously at a daily dose of 20mg, formulated in 40mg of mannitol.

Parameters of visual impairment were measured in the opthalmically acceptable manner as known in the art.
Visual impairment was assessed at six monthly intervals and the total change over the two year period examined.

Results

61 patients completed the full two years of the study. Of these patients, 29 did not experience any relapse of MS during the two years.

Out of the patients experiencing a relapse of MS whilst being treated with copolymer-1, those who had previous experience of optic neuritis (ON) had a 50% chance of having a further ON experience; Patients who had no previous history of ON had a 1 in 14 chance of developing ON. These chances are considerably lower than would normally have been expected had these patients

not been receiving copolymer-1.

Table 1 below shows that in all visual parameters assessed there was a prevention in the deterioration in visual impairment and in many instances there was an improvement as compared to the degree of visual impairment at the commencement of the study. (RE= right eye, LE= left eye)

Table 1

		Improved	No change	Worsened	Total tested
Visual acuity	RE	8	43	6	57
	LE	9	44	4	57
Optic Disc	RE	11	38	10	59
	LE	15	40	4	59
Pupil Reaction	RE	11	40	8	59
	LE	7	46	6	59
Visual Field	RE	6	53	0	59
	LE	4	53	2	59
Ocular Motility	RE	2	53	6	61
	LE	2	54	5	61

CLAIMS

1. The use of copolymer-1 in the manufacture of a medicament for the treatment of visual impairment associated with multiple sclerosis.

2. The use of copolymer-1 in the manufacture of a medicament for the treatment of optic neuritis.

3. The use of copolymer-1 in the manufacture of a medicament for the treatment of visual impairment associated with optic neuritis.

4. The use of copolymer-1 in the manufacture of a medicament for use in slowing the deterioration of visual impairment in optic neuritis.

5. A method of treating a patient suffering from visual impairment related to multiple sclerosis, comprising administering to said patient a therapeutically effective amount of copolymer-1.

6. A method of treating a patient suffering from optic neuritis, comprising administering to said patient a therapeutically effective amount of copolymer-1.

7. The use according to any of Claims 1 to 4 wherein the medicament contains 20mg copolymer-1.

8. The method according to any of Claims 5 to 6 comprising daily administration of 20mg copolymer-1.

INTERNATIONAL SEARCH REPORT

Internat Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE NEUROLOGICAL SCIENCES, vol. 31, no. 3, 1977 pages 433-438, ODED ABRAMSKI ET AL. 'Effect of a synthetic polypeptide (COP 1) on patients with multiple sclerosis and with acute disseminated encephalomyelitis' cited in the application	1,5
Y	see abstract see table 1 ---	2-4,6-8
X	CLINICAL NEUROPHARMACOLOGY, vol. 10, no. 5, 1987 pages 389-396, LOREN A. ROLAK 'Copolymer-I therapy for multiple sclerosis'	1,5
Y	see page 391, paragraph 4 ---	2-4,6-8
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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AM. FAM. PHYS., vol. 48, no. 2, 1993 pages 273-276, MARK J. RIEUMONT ET AL. 'Neuroimaging evaluation in multiple sclerosis' see page 273, right column see page 276, left column	2-4,6-8
Y	PROC. NATL. ACAD. SCI. USA, vol. 91, no. 11, May 1994 pages 4872-4876, MASHA FRIDKIS-HARELI ET AL. 'Direct binding of myelin basic protein and synthetic copolymer 1 to class II major histocompatibility complex molecules on living antigen-presenting cells---specificity and promiscuity' see abstract	2-4,6-8
Y	ROBERT BERKOW ET AL. 'The Merck Manual of Diagnosis and Therapy' 1992 , MERCK RESEARCH LABORATORIES , RAHWAY N.J. see page 2392 - page 2393	2-4,6-8

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